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EDITORIAL

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Neuromuscular conditions in the intensive care unit

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Three articles in this issue address neuromuscular conditions in the intensive care unit (ICU). Two focus on critical illness polyneuropathy and the third on neuromuscular blocking agents.

Critical illness polyneuropathy (CIP), a complication of sepsis and multiple organ failure [1], should be regarded as a common occurrence in ICUs throughout the world. It usually presents with difficulty in weaning from the ventilator, but in only half of the patients are there clearcut neurological signs of a polyneuropathy. Thus it remains an occult condition in most ICUs. Electrophysiological studies are necessary for diagnosis. Morphological studies indicate the presence of a primary axonal motor and sensory polyneuropathy without inflammatory change [1]. If the septic syndrome can be treated successfully, recovery from the polyneuropathy occurs in weeks in mild cases and in months in more severe cases. CIP has been reviewed by Leitjen and de Weerd [3] and by Bolton [4].

Recent publications in the literature have challenged this uniform description of CIP. A pure axonal motor neuropathy has been described as a regular complication of neuromuscular blocking agents [5]. A thick filament myopathy has also been described, usually in asthmatic patients when they receive neuromuscular blocking agents and steroids to control a particularly severe attack. Muscle biopsy shows a loss of thick filaments centrally in the muscle fiber [6]. It has been suggested that patients originally thought to have CIP may instead have had a myopathy or possibly a combination of both – a polyneuromyopathy [7]. Finally, two prospective studies relying on clinical examination of ICU patients failed to encounter critical illness polyneuropathy [8, 9].

The study by Berek et al. [10] at the University Hospital, Innsbruck, Austria, reaffirms CIP as a distinctive clinical entity of considerable importance in ICU management. Twenty-two patients who had sepsis (or the systemic inflammatory response syndrome) and multiple organ failure were assessed by serial neurological examinations and electrophysiological studies. The incidence of CIP was 73%, almost identical to that found in the prospective study of Witt et al. [2]. Moreover, none of the patients had received steroids or neuromuscular blocking agents, and on electrophysiological studies none had evidence of a primary myopathy. Creatinine phosphokinase levels were normal or midly elevated, providing no evidence for a significant necrosis of muscle. Difficulty in weaning from the ventilator was an important early clinical sign. However, since the clinical examination was often equivocal, the authors strongly recommended electrophysiological studies to establish the diagnosis. They also recommended that such studies should be performed in patients with sepsis if a polyneuropathy was suspected clinically, or if there were unexplained weaning problems.

Leijten and De Weerd [11] in the Westeinde Hospital, The Hague. The Netherlands, used different methods of analysis than Berek et al. [10]. They studied 38 patients who were on mechanical ventilation for more than 7 days. Electrophysiological studies revealed that 18 of 38 suffered from CIP (an incidence of 50%), and in these patients with polyneuropathy there was an increased incidence of multiple organ dysfunction and of time on mechanical ventilation. However, they report that the time of weaning, while longer in the patients with CIP [mean range 6.5 (1–48) for no CIP versus 9.5 (1–38) for CIP], was surprisingly statistically no different than patients who did not have CIP. Our own studies [12] and those of

Berek et al. [10] indicate that CIP remains an important neuromuscular cause of prolonged ventilation and difficulty in weaning from the ventilator.

In the report by Appadu et. al. [13] from the Leicester Royal Infirmary a postal survey was utilized to determine patterns of practice in the use of neuromuscular blocking agents in the intensive care unit setting in the United Kingdom. All respondents used these agents to facilitate mechanical ventilation or treat increased intracranial pressure. Of these, 60% utilized continuous infusion, but 90% relied only on clinical methods to assess the degree of muscle weakness, instead of peripheral nerve electrical stimulation. The intermediary acting vecuronium or atracurium were used most commonly, but the authors did not question whether side affects were being observed. The literature indicates that vecuronium or pancromium bromide have been most commonly associated with an axonal motor polyneuropathy or a myopathy, both being reversible after discontinuation of the drug. Most agree with Appadu et al. [13] that because of these possible toxic side affects the drug should be used for a shorter period of time and in as low a dose as possible. Nonetheless, there is still no proof of the toxicity of these neuromuscular blocking agents. Neither neuromuscular blocking agents nor steroids were used in any of the patients reported by Berek et al. [10]. Lieghten et al. [11], observed no association between the use of vecuronium and the incidences of CIP. Results from our own unit have been similar. While further prospective studies are needed to address this and other issues, it seems likely that neuromuscular blocking agents and steroids may singly or in combination have toxic effects on peripheral nerve and muscle. Many reports tend to discount the effects of sepsis. However, it is my view that sepsis is often an important underlying factor, even in patients with acute asthma. Thus, in addition to sepsis-induced changes in the microvasculature with impaired perfusion of peripheral nerve, there is increased permeability of capillaries. Toxic substances or their metabolites, including neuromuscular blocking agents and steroids, could thereby gain entry to both peripheral nerve and muscle [4].

It is worthwhile reviewing the approach to patients in the ICU who have weakness of limb and respiratory muscles (Table 1) [14]. The problem should be considered in two main categories. First are those patients who develop paralysis rapidly before admission to the critical care unit. Because of the acuteness of the situation there is not sufficient time for investigation of the underlying cause until stabilization has been achieved in the ICU. Conditions to be considered are high cervical spinal cord dysfunction due to trauma, neoplasm, or infection, motor neuron disease in which the respiratory muscles are affected before the other muscles, Guillain-Barré syndrome and other acute polyneuropathies such as porphyria, the acute axonal forms of Guillain-Barré syndrome, including the pure motor variety particularly common in northern China [15]. Mild, chronic polyneuropathies such as diabetic polyneuropathy may affect predominantly the nerves of respiration, or after admission to the ICU sepsis may worsen a preexisting polyneuropathy. Occasionally defects in neuromuscular transmission, myasthenia gravis, and Lambert-Eaton myasthenic syndrome present with primary respiratory failure. Finally, there are myopathies, particularly those susceptible to a variety of insults, which may trigger necrotic myopathy and often myoglobinuria.

Table 1 Differential diagnosis in the ICU of rapidly developing paralysis involving respiratory muscles

Before admission to the ICU	After admission to the ICU
Disorders of the spinal cord	
Traumatic myelopathy	
Acute epidural compression due to neoplasm, infection	
Acute transverse myelitis	
Motor neuron disease	
Acute polyneuropathy	
Guillain-Barré syndrom	Critical illness polyneuropathy
Axonal form of Guillain-Barré	Motor neuropathy (N-M blockers)
Chronic polyneuropathy	
Chronic inflammatory demyelinating polyneuropathy	Chronic polyneuropathies plus sepsis
Diabetic polyneuropathy	
Neuromuscular transmission defects	
Myasthenia gravis	N-M blockers
Lambert-Eaton myasthenic syndrome	
Hypocalcemia	
Hypermagnesemia	
Organophosphate poisoning	
Wound botulism	
Tick bite paralysis	
Myopathy	
Muscular dystrophy – Duchenne's, myotonic, etc.	Cachectic myopathy
Acute necrotizing myopathy – myoglobinuria	The necrotizing myopathy of intensive care
	Thick filament myopathy

The second category are patients who have been admitted to the ICU for severe, primary illnesses or trauma and later develop neuromuscular disease. Foremost among these is CIP, but also to be considered are axonal motor neuropathies induced by neuromuscular blocking agents, thick filament myopathy, and transient neuromuscular transmission disorders complicating the use of neuromuscular blocking agents. If difficulty in weaning from the ventilator occurs, we have found that phrenic nerve conduction and needle EMG of the diaphragm is the most specific method of identifying a neuromuscular cause [12]. Figure 1 shows an algorithm that can be adopted which systematically investigates disorders of the

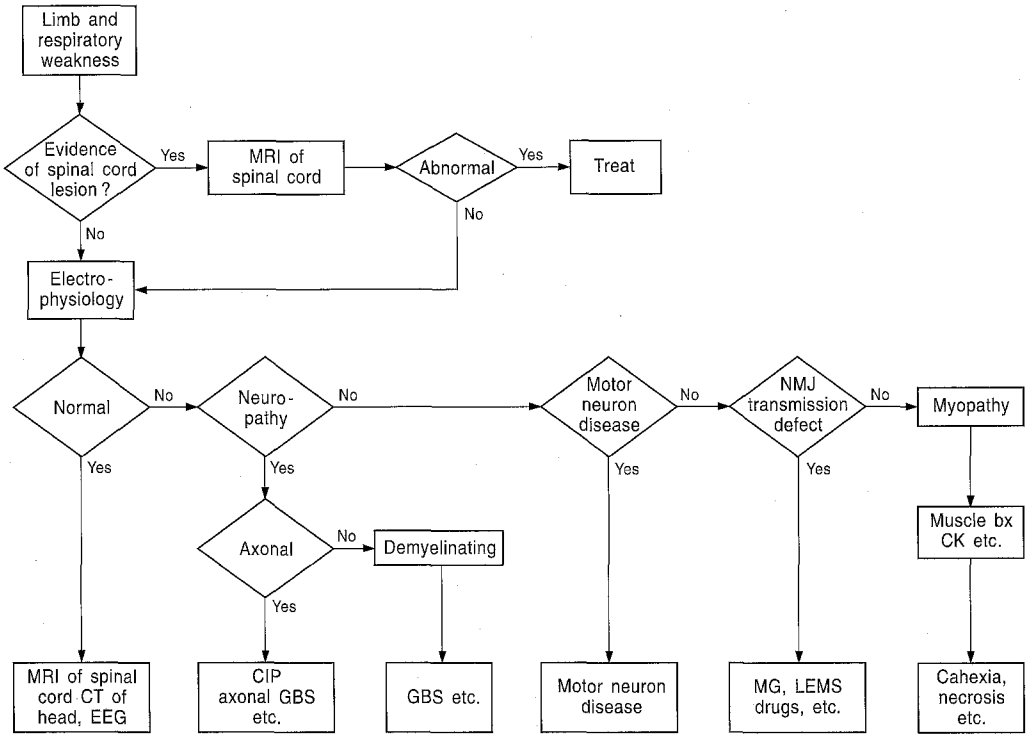

Fig. 1 An algorithm to guide the approach to investigation of ICU patients who have weakness of limb and respiratory muscles. *MRI*, Magnetic resonance imaging; *NMJ*, neuromuscular junction; *bx*, biopsy, *CK*, creatine phosphokinase; *CT*, computed tomography; *GBS*, Guillain-Barré syndrome; *MG*, myastenia gravis; *LEMS*, Lambert-Eaton myasthenia syndrome. (Adapted from Bolton [14])

spinal cord, peripheral nerve, neuromuscular junction and muscle. As emphasized by Berek et al. [10], this involves the close collaboration of neurologists, neurophysiologists, and intensivists. The results are important in specific treatment, such as the use of plasmapheresis and hyperimmune globulin to treat Guillain-Barré syndrome. They are also important in determining a long-term prognosis such as the indentification of motor neuron disease, which has a poor prognosis, or CIP in which the prognosis is usually good. The information is valuable, not only in counseling the patient and family but in studies of cost effectiveness in ICU management.

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